Remarks

These amendments and remarks are in response to the Office Action mailed September 20, 2005. Applicants cancel Claims 1, 3 and 9 – 12, and add new claims 13 -16.

Examiner Interview(s)

This Response is also in response to the Examiner Interview on September 14, 2005, which consisted of a telephone voice message and a fax from the Examiner. Applicants left a message for the Examiner on September 15, 2005, left a message for the Examiner on October 19, 2005 and received a second telephone voice message from the Examiner on October 20, 2005. In the facsimile, the Examiner indicated allowable subject matter as follows:

> Claim 13 (New). A pharmaceutical composition comprising a biocompatible carrier for injection or infusion and an isolated an purified N-terminal fragment of agglutinin-like sequence (ALS1) cell surface adhesion protein of *Candida albicans*, wherein the N-terminal fragment is encoded by a nucleotide sequence consisting of nucleotides 52 and 1296 of SEQ ID NO: 7 and wherein the composition produces antibodies that bind specifically to said ALS1 cell surface adhesion protein.
>
> Claim 14 (New). The composition of claim 1, wherein the N-terminal fragment contains the binding site of the ALS1 cell surface adhesin protein.

Accordingly, Applicants have amended the pending claims by canceling previously submitted claims and submitting four new claims numbered 13, 14, 15 and 16 including claims 13 and 14 verbatim as suggested by the Examiner.

The action of cancellation of all previous claims and the addition of new claims is likely to remove the basis for the Examiner's rejections in the September 20, 2005 Office Action. In order to be fully responsive, however, Applicants herewith consider the Examiner's remarks in order:

Rejections(s) under 35 U.S.C.§112, Second Paragraph

Regarding Examiner's paragraph 14:

(a). Applicants change reference to SEQ ID NO: 8 to SEQ ID NO. 7 in the new claims 13 -16 to better define Applicants' invention.

(b) and (c). Applicants remove the phrase 'effective immune response' from the new claims 13-16.

(d). Applicants correct the typographical error of 'No' to 'NO' in referring to 'SEQ ID NO' in the new claims 13-16.

(e). This rejection is moot with the cancellation of Claims 3, 9, 11 and 12.

Rejection(s) under 35 U.S.C.§ 102 (b)

Kraus et al. (1987)

In paragraph 15 of the 09/20/05 Office Action, the Examiner rejected claims 1 and 3 as being anticipated by Kraus *et al.* (J. Immunol. 139: 3084-3090, 1987).

The Examiner states that the N-terminal fragment recited in claim 1 has no structure or size limit, and thus even a single amino acid residue from SEQ ID NO: 8 or a dipeptide qualifies as an isolated and purified N-terminal fragment of SEQ ID NO: 8. The citation of Kraus (1987) was stated to be an example of a single amino acid and an adjuvant used for antibody production. Applicants' claims, however, as currently amended, define precisely the N-terminal fragment as nucleotide sequence consisting of nucleotides 52 to 1296 of SEQ ID NO: 7, which defines precisely the structure and size limit of the N-terminal fragment.

Kraus (1987) did not use the amino acid cysteine with adjuvant for antibody production. Instead, Kraus used a 22 amino acid M protein fragment with cysteine added at the C-terminal

end. This M protein peptide has no sequence similarity with the N-terminal ALS1 protein fragment. Further, neither Claims 1 and 3, nor new Claims 13-16 are anticipated under 35 U.S.C. § 102 (b) by Kraus *et al.* (1987), because Kraus *et al.* does not disclose every element of Applicants' invention as claimed. Applicants therefore respectfully request withdrawal of this 35 U.S.C. § 102 (b) rejection.

Anticipation:

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California* 814 F.2d 628, 631, (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ...claim." *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226 (Fed. Cir. 1989) (See MPEP § 2131).

The Examiner states that Kraus *et al.*(1987) teaches a pharmaceutical composition comprising an adjuvant and a cysteine residue. Examiner states that the cysteine residue qualifies as an isolated and purified N-terminal fragment of SEQ ID NO:8 of *C. albicans,* because the prior art cysteine residue constitutes an N-terminal fragment situated at position 73 of the instantly recited SEQ ID NO: 8. Applicants respectfully traverse.

First, there is absolutely no sequence similarity in the N-terminal region between the Type I Streptococccal M protein fragment synthesized by Kraus *et al.* (1987) and the *Candida albicans* ALS1 protein in Applicants' invention. The *Streptococcal* M protein and the *Candida albicans* ALS1 protein are two different and distinct proteins.

Secondly, Kraus used a protein fragment that was a chemically synthesized 22 amino acid fragment (residues 1-20 plus residues 24-26) with cysteine added to promote dimerization,

as well as conjugation to adjuvant. Cysteine as a single amino acid was not used as an antigen. The antigen used by Kraus was a 22 amino acid fragment of Streptococcal type I M protein that had cysteine added to the C-terminus. Kraus *et al.* studied the N-terminal sequence of type I M protein from Streptococcus, as stated, "...An NH_2-terminal peptide containing residues 1-20 followed by residues 24-26 and a COOH-terminal cysteine was synthesized..." (p. 3085, column 1, 6th paragraph). The peptide used as antigen by Kraus et al. has no sequence similarity to any region of the N-terminal ALS1 protein. Further, C-terminal cysteine is not part of the Streptococcal sequence, but was added by Kraus *et al.* during chemical synthesis for the purpose of dimerization and conjugation of the peptide to keyhole limpet hemocyanin (KLH). Kraus *et al.* used both conjugated and unconjugated peptides as antigens, but disclose,

> "...there were virtually no differences in the immune responses to the unconjugated and KLH-conjugated peptides. It should be noted that the synthetic peptide contains a COOH-terminal cysteine residue with the potential of forming disulfide bonds between peptide chains, resulting in dimers...Whether the 23-residue NH_2 would be immunogenic without the COOH-terminal cysteine requires further study." (p. 3089, column 2, paragraph 1, line 5).

For the Examiner to assert a single amino acid combined with adjuvant could function as an antigen in Applicants' invention does not take into account known and accepted principles in immunology regarding protein tertiary structure and epitopes involved in immunological response to an antigenic stimulus. It is highly likely that more than one amino acid is necessary in the N-terminal ALS1 protein fragment to produce antibodies that recognize *Candida albicans* with sufficient specificity to block adherence of *C. albicans* to constitute a pharmaceutical composition according to Applicants' invention. Antibodies raised against cysteine would not be expected by one with skill in the art to prevent binding of *C. albicans* to endothelial cells.

Applicants' amended claims clearly define the N-terminal region of the ALS1 protein, which Applicants have established contains the *C. albicans* adhesion site. As discussed above, Applicants' claims as amended are not anticipated by Kraus *et al.* (1987) because Applicant's have defined precisely the region of the N-terminal ALS1 protein to be used as antigen. Applicants therefore respectfully request the withdrawal of this rejection.

Rejection(s) under 35 U.S.C.§ 102 (b)

Hoyer, et al., J. Bacteriol. 180: 5334-5343, October 1998; Hoyer, 1998, of record

In paragraph 16, the Examiner states that claims 1, 3, 10 and 11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hoyer et al. (1998). Examiner states that claims 1 and 3 do not define the claimed N-terminal fragment by its structure or amino acid composition, and do not place a size or structure limited on the recited N-terminal fragment. Applicants respectfully traverse.

Claims 1, 3, 10 and 11 are cancelled. Newly presented claims 13-16 define the N-terminal fragment of *C. albicans* ALS1 protein by nucleotide number (SEQ ID NO. 7).

Secondly, the N-terminal fragment of the ALS1 protein is known to contain the adhesion binding site of *C. albicans.*

Applicants have argued consistently that the partially purified mixture of ALS1p and yeast proteins in PBS as taught by Hoyer et al. (1998) is not the isolated and purified protein fragment in a biocompatible carrier as claimed by Applicants (see Response 1/18/05, pages 5, paragraph 3 to page 8; Response 7/1/05, page 6, paragraph 3 to page 7; and Response 6/18/04, page 4, paragraph 4). When Hoyer has a partially purified preparation of the N-terminal fragment of ALS1 protein in PBS, Hoyer describes other proteins as being present. The Hoyer

preparation, therefore is only partially purified, and constitutes a mixture of proteins, prior to electrophoretic separation. Applicants, however, claim an isolated and purified protein fragment of ALS1 in a biocompatible carrier as a pharmaceutical composition to elicit a specific antigenic response. Hoyer (1998) does not teach an isolated and purified N-terminal fragment in PBS, only a protein mixture. Therefore, Applicants' claims are not anticipated by Hoyer (1998).

Applicants have previously asked Examiner for a showing that Hoyer's partially purified mixture would give the same antigenic response as isolated and purified protein. Mixtures of proteins do not meet the accepted biochemical standard of an isolated and purified protein, especially given the complexities of a specific immunological response for a pharmaceutical composition, such as claimed in Applicants' invention. For the above reasons, Applicants' claims are not anticipated by Hoyer (1998). Applicants respectfully request the withdrawal of this rejection.

I. Conclusion

Prompt and favorable action on the merits of the claims is earnestly solicited. Should the Examiner have any questions or comments, the undersigned can be reached at (949) 567-6700.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 15-0665.

Respectfully submitted,

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By: _____

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